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Ruthenium-Catalyzed Reactions of 1-Cyclopropyl-2-propyn-1-ols with Anilines and Water via Allenylidene Intermediates: Selective Preparation of Tri- and Tetrasubstituted Conjugated Enynes

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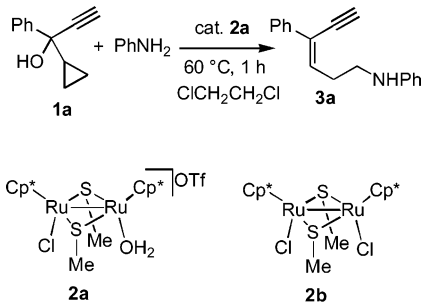
Abstract: Ruthenium-catalyzed efficient preparation of the conjugated enynes can be carried out in the reactions of 1-cyclopropyl-2-propyn-1-ols with nitrogen- and oxygen-centered nucleophiles such as anilines and water in the presence of a catalytic amount of sulfur-bridged diruthenium complexes. The use of such complexes as catalysts realizes the completely stereoselective preparation of tri- and tetrasubstituted conjugated enynes, where ruthenium−allenylidene complexes work as key intermediates. The direct attack of nucleophiles on a cyclopropane ring connected to an allenylidene ligand is a key step to obtain the enynes stereoselectively.

Introduction

The conjugated enynes are one of the most versatile intermediates in synthesis for organic materials.[1] A number of useful strategies are now available, but the number of reports of highly selective preparation of conjugated enynes is quite limited due to the competitive formation of undesired regio- and stereoisomers. Therefore, a novel and efficient method for selective preparation of tri- and tetrasubstituted conjugated enynes should be developed from a synthetic viewpoint.

Since the first discovery of the transition metal−allenylidene complexes in 1976, they have attracted a great deal of attention as a new type of organometallic intermediate.[2] Interesting and unprecedented reactivity of allenylidene complexes has so far been developed, but almost all of them are limited to stoichiometric reactions except for a few examples.[2] As an extension of our study on the development of novel catalytic reactions via ruthenium−allenylidene intermediates,[3] we have now envisaged to develop the ruthenium-catalyzed reactions of 1-cyclopropyl-2-propyn-1-ols with nucleophiles affording the corresponding conjugated enynes in high yields with an excellent selectivity. Here, the reaction is expected to occur via an attack of nucleophiles on a cyclopropane ring connected to an allenylidene ligand. The present paper describes some successful results of this novel catalytic reaction.

Scheme 1



Results and Discussion

Treatment of 1-cyclopropyl-1-phenyl-2-propyn-1-ol (**1a**; 1 equiv) with aniline (10 equiv) in the presence of a catalytic amount of a sulfur-bridged diruthenium complex [Cp*RuCl-

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(1) For recent examples, see: (a) Liu, Y.; Nishiura, M.; Wang, Y.; Hou, Z. *J. Am. Chem. Soc.* **2006**, *128*, 5592. (b) Pahadi, N. K.; Camacho, D. H.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 1152.
(2) For recent reviews, see: (a) Cadierno, V.; Gamasa, M. P.; Gimeno, J. *Eur. J. Inorg. Chem.* **2001**, 571. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176.
(3) (a) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433. (b) Onodera, G.; Matsumoto, H.; Nishibayashi, Y.; Uemura, S. *Organometallics* **2005**, *24*, 5799. (c) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715. (d) Ammal, S. C.; Yoshikai, N.; Inada, Y.; Nishibayashi, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 9428. (e) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, 881. (f) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Organometallics* **2006**, *25*, 35. (g) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835.

Table 1. Ruthenium-Catalyzed Reaction of 1-Cyclopropyl-1-phenyl-2-propyn-1-ol (**1a**) with Aniline in the Presence of Thiolate-Bridged Diruthenium Complex (**2a**)[a]

	reaction conditions		
run	temp	time (h)	yield of **3a** (%)[b]
1	60 °C	1	89
2	room temp	2	77
3[c]	60 °C	1	78
4[d]	60 °C	1	32

[a] All reactions of **1a** (0.25 mmol) with aniline (2.50 mmol; 10 equiv to **1a**) were carried out in the presence of **2a** (0.0075 mmol) in $ClCH_2CH_2Cl$ (2.5 mL). [b] Isolated yield. [c] Aniline (0.50 mmol; 2 equiv to **1a**) was used. [d] **2b** (0.0125 mmol) was used together with NH_4BF_4 (0.025 mmol) in place of **2a**.

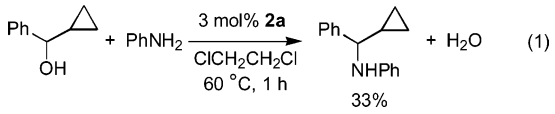
Table 2. Ruthenium-Catalyzed Reactions of 1-Cyclopropyl-2-propyn-1-ols (**1**) with Anilines in the Presence of **2a**[a]

run	propargylic alcohol **1** (Ar)	aniline	yield of 3, (%)[b]
1	**1b**, *p*-MeC_6H_4	$PhNH_2$	**3b**, 73[c] (83)
2	**1c**, *p*-$MeOC_6H_4$	$PhNH_2$	**3c**, (65)
3	**1d**, *p*-FC_6H_4	$PhNH_2$	**3d**, 63 (80)
4	**1e**, *p*-ClC_6H_4	$PhNH_2$	**3e**, 66 (83)
5	**1f**, 2-thienyl	$PhNH_2$	**3f**, (45[c])
6	**1a**, Ph	*p*-$MeC_6H_4NH_2$	**3g**, (75)
7	**1a**, Ph	3,5-$Me_2C_6H_3NH_2$	**3h**, (67[d])
8	**1a**, Ph	*p*-$FC_6H_4NH_2$	**3i**, 68 (80)
9	**1a**, Ph	*p*-$ClC_6H_4NH_2$	**3j**, 68 (78)
10	**1a**, Ph	*p*-$MeOC(O)C_6H_4NH_2$	**3k**, 69 (78)
11	**1a**, Ph	*o*-$MeOC(O)C_6H_4NH_2$	**3l**, (71)
12	**1a**, Ph	*p*-$CF_3C_6H_4NH_2$	**3m**, 66 (82)
13	**1a**, Ph	PhNHMe	**3n**, 75[e] (82[e])
14	**1a**, Ph	Ph_2NH	**3o**, 39[e] (52[e])

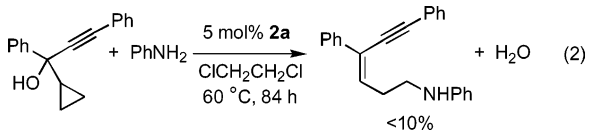
[a] All reactions of **1** (0.25 mmol) with aniline (0.50 mmol; 2 equiv to **1**) were carried out in the presence of **2a** (0.0075 mmol) in $ClCH_2CH_2Cl$ (2.5 mL) at 60 °C for 1 h. [b] Isolated yield. The value in parentheses is the isolated yield of the reaction with aniline (2.50 mmol; 10 equiv to **1**). [c] For 3 h. [d] For 6 h. [e] **2a** (0.0125 mmol; 5 mol % to **1**) was used and for 24 h.

(μ_2-SMe)$_2$RuCp*(OH$_2$)]OTf[4] (Cp* = η^5-C_5Me_5; OTf = OSO_2CF_3; **2a**) (3 mol %) in $ClCH_2CH_2Cl$ at 60 °C for 1 h afforded the (*E*)-1,3-enynes (**3a**, *E* only) in 89% isolated yield with a complete selectivity (Scheme 1; Table 1, run 1). No stereoisomers were detected by ^{1}H NMR. The reaction proceeded smoothly even at room temperature only with a slight decrease in the product yield (Table 1, run 2). Even the use of 2 equiv of aniline to **1a** worked well with only a slight decrease of **3a** (Table 1, run 3). This catalytic reaction also proceeded smoothly when the corresponding neutral diruthenium complex [Cp*RuCl(μ_2-SMe)]$_2$[4] (**2b**) was used as a catalyst together with NH_4BF_4 (Table 1, run 4). Interestingly, the reaction did not proceed at all in the presence of a catalytic amount of other transition metal salts and Brønsted acid such as $AuCl_3$, $FeCl_3$, and *p*-toluenesulfonic acid.[5]

Catalytic reactions of other propargylic alcohols (**1**) with aniline were investigated by using **2a** as a catalyst. Typical results are shown in Table 2. The presence of an aryl moiety at the propargylic position of propargylic alcohols was revealed to be necessary for obtaining the corresponding conjugated (*E*)-enynes (**3**) effectively (Table 2, runs 1−4).[6] The use of 10 equiv of aniline to **1** increased the yield of **3** in all cases. The use of the 2-thienyl moiety in place of the benzene group in propargylic alcohol decreased the product yield (Table 2, run 5). On the other hand, reaction of 1-cyclopropyl-1-phenylmethanol with aniline in the presence of a catalytic amount of **2a** did not give any ring-opening products, and only the benzylic substituted product was obtained (eq 1). Also, reaction of propargylic



alcohol bearing an internal alkyne moiety with aniline did not proceed smoothly, the corresponding enyne being obtained in <10% yield even for a longer reaction time (eq 2).[8] These results



indicate that *a terminal alkyne moiety in the propargylic alcohol works as a trigger to promote the carbon−carbon bond cleavage of a cyclopropane ring.*

Next, reactions with other nucleophiles were carried out under the same reaction conditions. A variety of anilines were revealed to be available as nucleophiles to give the corresponding 1,3-enynes in good to high yields (Table 2, runs 6−12). In contrast, reactions of *N*-substituted anilines such as *N*-methylaniline and *N*,*N*-diphenylamine were sluggish (Table 2, runs 13 and 14). Unfortunately, the use of alkylamines and amides such as benzylamine, butylamine, acetamide, and benzenesulfonamide was in vain although amides were known to work as nucleophiles in the propargylic substitution reactions catalyzed by **2**.[3a]

Reactions of some propargylic alcohols in water also proceeded smoothly to give the corresponding conjugated (*E*)-enynes in good to high yields. Typical results are shown in Table 3. It was clearly confirmed that water works as a nucleophile when $H_2{}^{18}O$ was used as solvent (Table 3, run 2). Thus, we have newly found that water can be used as a nucleophile in the reactions accompanied by ring opening. This is the first successful example of catalytic reactions with water, where allenylidene complexes are considered to be important intermediates.

In order to obtain some information about the reaction pathway, the following stoichiometric and catalytic reactions were investigated. Treatment of **2a** with a stoichiometric amount of **1a** in tetrahydrofuran (THF) at room temperature for 30 min gave the corresponding allenylidene complex bearing a cyclo-

(4) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 5100 and references therein.

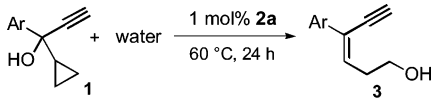
(5) Some metal salts and Brønsted acid were reported to work as catalysts for the propargylic substitution reactions; see: (a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (b) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298. (c) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383. (d) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

(6) The stereochemistry of some enyne products was determined by X-ray analysis. See the Supporting Information for experimental details.

(7) See the Supporting Information for experimental details.

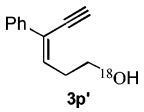
(8) (a) For a review of cyclopropylmethyl cations, see: Richey, H. G., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. V. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, Chapter 25. (b) Childs, R. F.; Kostyk, M. D.; Lock, C. J. L.; Mahendran, M. *J. Am. Chem. Soc.* **1990**, *112*, 8912.

Table 3. Ruthenium-Catalyzed Reactions of 1-Cyclopropyl-2-propyn-1-ols (**1**) with Water in the Presence of **2a**[a]



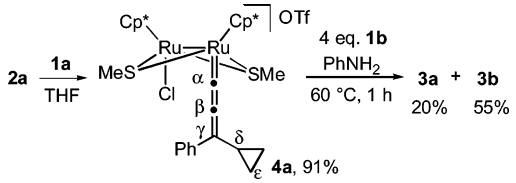
run	propargylic alcohol **1** (Ar)	water	yield of **3**, (%)[b]
1	**1a**, Ph	H_2O	**3p**, 87
2	**1a**, Ph	$H_2{}^{18}O$	**3p′**, 62
3	**1b**, *p*-MeC_6H_4	H_2O	**3q**, 77
4	**1d**, *p*-FC_6H_4	H_2O	**3r**, 70[c]

[a] All reactions of **1** (0.25 mmol) were carried out in the presence of **2a** (0.0025 mmol) in water (2.5 mL) at 60 °C for 24 h. [b] Isolated yield. [c] **2a** (0.0075 mmol; 3 mol% to **1**) was used.

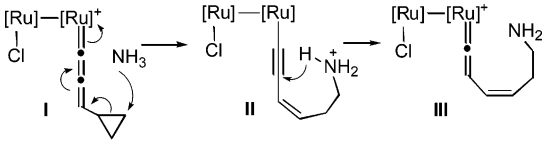


propyl group at the γ-position of the allenylidene moiety (**4a**) in 91% isolated yield. The structure of the complex was unambiguously characterized by X-ray crystallography (Scheme 2),[7] where a slightly longer bond distance such as 1.511(6) Å was observed between the δ- and ϵ-carbons of the cyclopropane ring. Reaction of **4a** with aniline in the presence of other propargylic alcohol (**1b**) afforded the corresponding enyne (**3a**) in 20% yield together with **3b** in 55% yield. Furthermore, reaction of **2a** with aniline in the presence of a catalytic amount

Scheme 2



Scheme 3



of **4a** at 60 °C for 1 h afforded **3a** in 83% yield. These results indicate that the catalytic reaction might proceed via **4a** as a key intermediate.

By taking into consideration the product structure, the nucleophilic attack should occur on the ϵ-carbon of a cyclopropane of the intermediate allenylidene complex like **4a**. In order to know whether this process followed by ring opening is energetically favorable or not, we investigated the density functional theory calculation at the B3LYP/LANL2DZ level of theory for the model reaction of $[CpRuCl(\mu_2\text{-}SMe)_2RuCp(=C=C=CH(CHCH_2CH_2))]^+$ (**I**; Cp = η^5-C_5H_5) with NH_3.[7] The relative energy diagram and optimized structures are shown in Figure 1. As shown in Figure 1, the expected nucleophilic attack of NH_3 on the ϵ-carbon of a cyclopropane ring connected to an allenylidene moiety was revealed to occur easily to give the

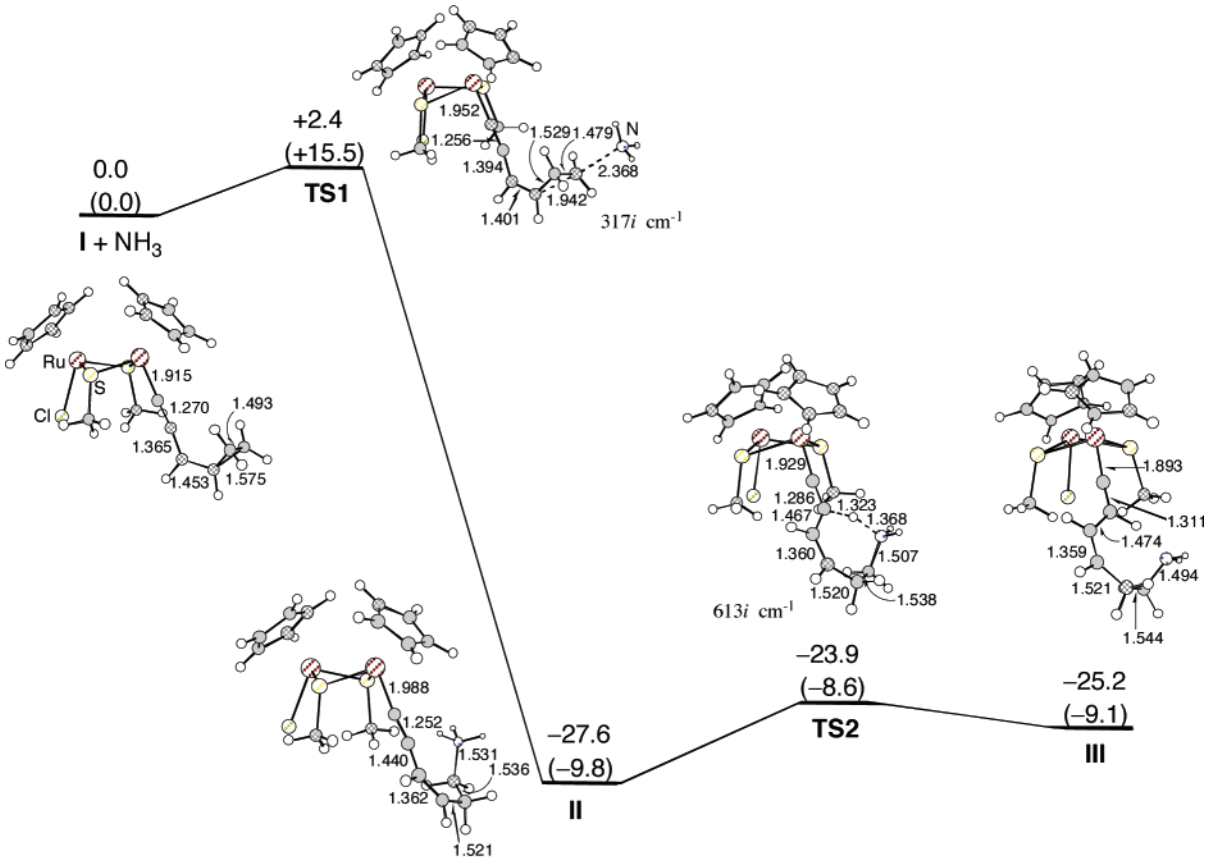
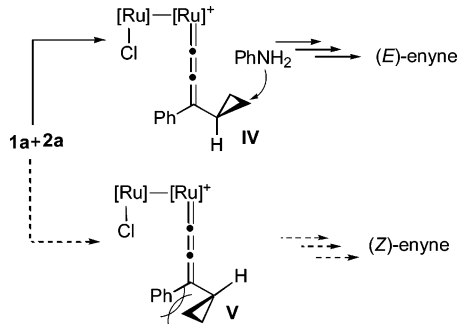


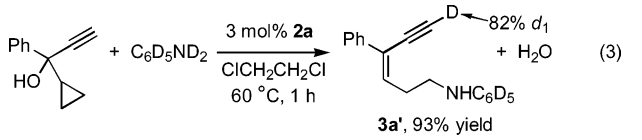
Figure 1. Relative energy diagram (kcal/mol) for the model reaction of **I** with NH_3 at the B3LYP/LANL2DZ level of theory. Values in parentheses are relative free energies at 298.15 K. Bond lengths in structures are in angstroms.

Scheme 4



corresponding ruthenium−alkynyl complex (**II**). Then, it is followed by the smooth transfer of one of the protons on the nitrogen atom into the alkynyl moiety to give the corresponding vinylidene complex (**III**). This result indicates that such reaction pathway as that shown in Scheme 3 is energetically favorable and reasonable.

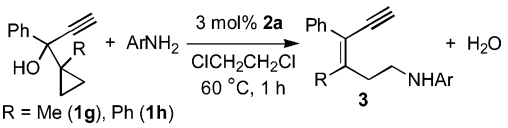
Further, the relative reactivity (the Hammett linear free-energy relationship) of substituted anilines ($X-C_6H_4NH_2$, X = *p*-Me, H, *p*-Cl) with propargylic alcohol (**1a**) in the presence of **2a** was determined from the relative rates of the conversion of **1a** when conversions were low (<10%).[7] The rate data correlated well with the Hammett linear free-energy relationship with use of σ values. Better correlation ($\rho = +1.67$) was obtained with a σ^+. These results also support the reaction pathway where a nucleophile attacks first on a cyclopropyl group as shown in Scheme 3. Thus, the reaction with *p*-chloroaniline, whose conjugated acid has a high acidity, proceeded more smoothly because the proton transfer should take place rapidly in the second step of Scheme 3. Moreover, supplemental support for this mechanism was provided by the finding that the enyne-d_1 (**3a**-d_1) was obtained in 93% yield with 82% deuterium incorporation at the C-1 position when **1a** was treated with aniline-d_7 in the presence of **2a** (eq 3). Separately, it was



confirmed that no deuterium exchange occurred in the reactions of other propargylic compounds bearing a terminal alkyne moiety with aniline-d_7, showing that the deuterium incorporation at the C-1 position is due to the proton transfer in the proposed reaction pathway as shown in Scheme 3.

To account for highly selective formation of (*E*)-enynes (**3a**), we propose a reaction pathway as shown in Scheme 4. The steric repulsion between a phenyl group and a cyclopropyl moiety might give a predominant formation of **IV** which is susceptible to nucleophilic attack of aniline on the cyclopropane ring to give (*E*)-enynes with a complete selectivity. It is well-known that the interaction of the cyclopropyl bonding orbitals with the carbon p orbital of the carbocation imposes a preference for the bisected conformation (the eclipsed conformation) of the cyclopropylmethyl cation in comparison with the perpendicular conformation.[8] A similar stabilization between cyclopropyl bonding orbitals and the p orbital of the γ-carbon in the allenylidene ligand may also occur in **IV** as shown in Scheme 4.

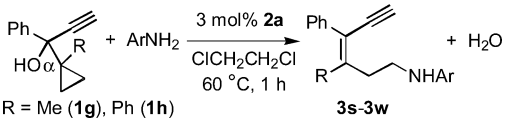
Table 4. Ruthenium-Catalyzed Reactions of 1-Cyclopropyl-2-propyn-1-ols (**1**) with Anilines in the Presence of **2a**[a]



run	propargylic alcohol (**1**)	$ArNH_2$ (equiv)	yield of **3**, (%)[b]	ratio of *E*/*Z* isomers
1	**1g**	$PhNH_2$	**3s**, 58 (85)	>99/<1
2	**1g**	*p*-$MeC_6H_4NH_2$	**3t**, 60 (84)	98/2
3	**1g**	*p*-$FC_6H_4NH_2$	**3u**, (83)	98/2
4	**1g**	*p*-$ClC_6H_4NH_2$	**3v**, (82)	98/2
5	**1h**	$PhNH_2$	**3w**, 65[c] (80[c])	>99/<1[d]

[a] All reactions of **1** (0.25 mmol) with aniline (0.50 mmol; 2 equiv to **1**) were carried out in the presence of **2a** (0.0075 mmol) in $ClCH_2CH_2Cl$ (2.5 mL) at 60 °C for 1 h. [b] Isolated yield. The value in parentheses is the isolated yield of the reaction with aniline (2.50 mmol; 10 equiv to **1**). [c] For 2 h. [d] *Z*/*E* = >99/<1.

Scheme 5



For synthetic application, the selective preparation of tetrasubstituted enynes was also investigated in the reactions of 1-cyclopropyl-2-propyn-1-ols bearing a substituent at the α-position in a cyclopropane ring (**1g** and **1h**) with anilines (Scheme 5). As expected, the corresponding tetrasubstituted enynes (**3s**−**3w**[9]) were obtained in high yields with an almost complete selectivity. Typical results are shown in Table 4. Here, the use of 10 equiv of anilines to **1** much increased the yield of **3**. The ring-opening reactions of cyclopropanols with nucleophiles are known as Julia olefin synthesis to afford the corresponding (*E*)-homoallylic derivatives predominantly, where halogen- and oxygen-centered nucleophiles are generally available.[10−12] In contrast, the reaction with nitrogen-centered nucleophiles described here provides the excellent stereoselective preparative method for tetrasubstituted conjugated enynes.

Conclusion

In summary, we have found that ruthenium-catalyzed preparation of the conjugated enynes in good to high yields with an excellent selectivity could be carried out in reactions of 1-cyclopropyl-2-propyn-1-ols with nitrogen- and oxygen-centered nucleophiles such as anilines and water in the presence of a catalytic amount of sulfur-bridged diruthenium complexes. The use of such complexes as catalysts realizes the completely stereoselective preparation of tri- and tetrasubstituted conjugated enynes, where ruthenium−allenylidene complexes work as key intermediates.

Acknowledgment. This work was supported by Grant-in-Aids for Scientific Research on Priority Areas (Nos. 18037012

(9) The (*Z*)-stereochemistry in **3w** is due to the nomenclature. We confirmed the stereochemistry of (*Z*)-**3w** by a preliminary X-ray analysis.
(10) For examples, see: (a) Morgan, E. D.; Thompson, L. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 399. (b) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2024.
(11) (a) Sakaguchi, K.; Higashino, M.; Ohfune, Y. *Tetrahedron* **2003**, *59*, 6647. (b) Honda, M.; Mita, T.; Nishizawa, T.; Sano, T.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2006**, *47*, 5751.
(12) Descoins, C.; Samain, D. *Tetrahedron Lett.* **1976**, *17*, 745.

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Supporting Information Available: Experimental and computational details, characterization data, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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